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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/047,693	01/09/2002	Istvan Bakondi-Kovacs	2664/47002	5182

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EXAMINER	
MARX, IRENE	
ART UNIT	**PAPER NUMBER**
1651	

DATE MAILED: 02/22/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/047,693	BAKONDI-KOVACS ET AL.	
	Examiner	Art Unit	
	Irene Marx	1651	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 December 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-27* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-27* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/30/04 has been entered.

Claims 1-27 are being considered on the merits.

Claims 28-31 are cancelled.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-27 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ott *et al.* (GB2,114,978) taken with Tomita *et al.*, Vanek *et al.*, BG 50996 and McIntyre *et al.*

The claims are directed to a fermentation process for producing 6'-0-carbamoyl tobramycin regulating constant levels of assimilable carbon and nitrogen sources.
Each of Ott *et al.* or Tomita *et al.* discloses a fermentation process for the production of 6'-0-carbamoyl tobramycin. See, e.g., Examples. Ott *et al.* discloses a variety of suitable carbon and nitrogen sources, including amino acids such as glutamic acid (See, e.g., page 2, line 55 to page 3, line 13). In addition Tomita *et al.* discloses a similar listing of suitable carbon, nitrogen and inorganic salts such as phosphate. See, e.g., col. 11, lines 7-51. The references appear to differ from the claimed invention in that "regulating constant levels of the assimilable carbon and nitrogen source levels" is not disclosed. However, the regulation of constant levels of carbon and nitrogen sources, by using fed-batch or continuous culturing processes, such as of a chemostat, to regulate constant levels of carbon, nitrogen and/or mineral salts is an old and well

known expedient in the fermentation arts and is the essence of biotechnical engineering. See, e.g., Vanek *et al.*, pages 191-195. In addition, the Bulgarian patent '996 and McIntyre *et al.* adequately demonstrate the use of regulation of carbon and nitrogen sources in the production of antibiotics with *Streptomyces,* respectively *S. tenebrarius* strains using a constant glucose and nitrogen feed (See, e.g., page 2, bridging paragraph between col. 1 and 2 and Figure 5, respectively). The Bulgarian patent is cited at page 14, paragraph 2 of the instant Specification. If applicants are in possession of a translation of this document, a copy thereof would be appreciated.

The process conditions discussed in the references appear to be substantially the same as those claimed. However, even if they are not, the adjustment of process conditions for optimization purposes identified as result-effective variables cited in the references would have been prima facie obvious to a person having ordinary skill in the art, since such adjustment is at the essence of biotechnical engineering. With respect to the ranges of carbon source and nitrogen source in dependent claims it is noted that the amounts in the claims are not clearly correlated to the strains cultured, timing of regulation and nature of the carbon and nitrogen sources and amounts thereof as used in the touted Examples 4 and 5.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to modify the process of Ott *et al.* and/or Tomita *et al.* by performing the fermentation process for the production of 6'-0-carbamoyl tobramycin in a fed-batch process, for example, as suggested by the teachings of Vanek *et al.* and McIntyre *et al.* to regulate constant levels of assimilable carbon, nitrogen and/or mineral salts for the expected benefit of maximizing the yield of the useful antimicrobial agent 6'-0-carbamoyl tobramycin.

Thus, the claimed invention as a whole was clearly *prima facie* obvious, especially in the absence of evidence to the contrary.

Response to Arguments

Applicant's arguments as they pertain to the above rejection have been fully considered but they are not deemed to be persuasive.

In response to applicant's argument that there is no suggestion to combine the references, the examiner recognizes that obviousness can only be established by combining or modifying the teachings of the prior art to produce the claimed invention where there is some teaching,

suggestion, or motivation to do so found either in the references themselves or in the knowledge generally available to one of ordinary skill in the art. In re Fine, 837 F.2d 1071, 5 USPQ2d 1596 (Fed. Cir. 19880; In re Jones, 958 F.2d 347, 21 USPQ2d 1941 (Fed. Cir. 1992). In this case, the primary references are directed to the production of the required tobramycin using assimilable carbon and nitrogen sources and the teaching references demonstrate that the fed-batch technique used in the instant method is old and well known in the art. Even though the McIntyre *et al.* reference produces a different antibiotic, it provides evidence to show that the use of regulation of constant levels of carbon and nitrogen source is old and well known in the art. It is of interest to note in this regard that the invention as claimed does not stipulate the level at which the constant level is adjusted, except in dependent claims and never for specific carbon and nitrogen sources simultaneously. Moreover, the timing or length of the "constant" period are not claim designated. In addition, the strain of microorganism fermented is not identified. One of ordinary skill in the art would have reasonably expected regulation at constant levels at least at some point during the fermentation, such as at the time of depletion of nutrients.

Regarding arguments that an "improved" yield is required, there is no clear claim designated limitation as to the level of improvement intended. Thus, this functional limitation includes infinitesimal "improvement in yield" and fails to add structure and significantly limit the claim.

In addition, and more importantly, the touted results argued at page 12 of the Response, wherein examples 4-5 are compared to examples 1-3, are not reflected in the claims of record. It is noted that the conditions to obtain any improvement in yield of tobramycin in the instant specification as filed require very specific process parameters. The cultivation requires constant regulation only after the 24th hour, wherein the culture is "fed", and a medium of specific and defined composition is added to specific strains *S. tenebrarius* NCAIM B(P) 000169 or NCAIM B(P) 000204. From the present record, there is no clear assurance that these strains are freely available to the public or that the results provided can be extrapolated to any microorganism or to any strain of *S. tenebrarius*. The effects of constant feeding at very low or at very high levels of carbon and nitrogen sources on tobramycin production with any microorganism cannot be readily assessed.

In the process exemplified in Examples 4 and 5 of the specification specific strains and a specific nutrient medium at a specific pH having specific carbon sources are cultured for specific cultivation periods, such as 18 hours. In addition, cultivation parameters include feeding done at the 24th hour; use of 50% sodium glutamate solution and 50% glucose solution. Phosphate content of the glucose solution was in the range of about 0.05 to about 0.2%. Feeding of these solutions were carried out from the 24th hour of the fermentation till the end by controlling in the production phase the glucose and glutamate content in the range of about 0.001 to about 0.05% and about 0.001 to about 0.1%, respectively. Additionally to the above concentrations, ammonia solution was also fed in order to control the ammonia nitrogen content in the range of about 30 to about 200 mg/100mL (i.e., about 0.03 to about 0.2%). None of these parameters are claim designated. It is noted that the specification emphasizes that the fed-batch technology used requires that the glucose, glutamate and ammonia nitrogen be regulated. See, e.g., page 13, paragraph 6.

The scope of the showing must be commensurate with the scope of claims to consider evidence probative of unexpected results, for example. In re Dill, 202 USPQ 805 (CCPA, 1979), In re Lindner 173 USPQ 356 (CCPA 1972), In re Hyson, 172 USPQ 399 (CCPA 1972), In re Boesch, 205 USPQ 215, (CCPA 1980), In re Grasselli, 218 USPQ 769 (Fed. Cir. 1983), In re Clemens, 206 USPQ 289 (CCPA 1980). It should be clear that the probative value of the data is not commensurate in scope with the degree of protection sought by the claim.

Therefore the rejection is deemed proper and it is adhered to.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Irene Marx whose telephone number is (571) 272-0919. The examiner can normally be reached on M-F (6:30-3:00).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 571-272-0926. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300 .

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Irene Marx
Primary Examiner
Art Unit 1651